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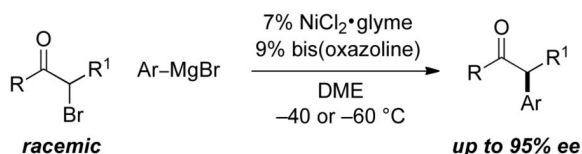
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Nickel/Bis(oxazoline)-Catalyzed Asymmetric Kumada Reactions of Alkyl Electrophiles: Cross-Couplings of Racemic α -Bromoketones

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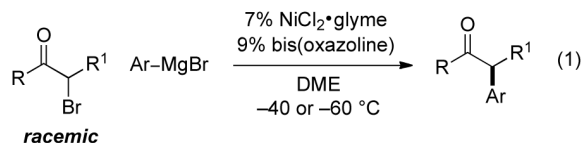
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Abstract



The first asymmetric Kumada reactions of alkyl electrophiles are described, specifically, cross-couplings of racemic α -bromoketones with aryl Grignard reagents. Several features of this investigation are of interest. First, the couplings proceed at remarkably low temperature ($-40\text{ }^{\circ}\text{C}$ or $-60\text{ }^{\circ}\text{C}$), which enables the asymmetric synthesis of racemization-prone α -arylketones. Second, dialkyl ketones undergo enantioselective coupling in good ee and yield. Third, readily available bis(oxazolines) are shown for the first time to be effective ligands for cross-couplings of alkyl electrophiles, thereby opening the door to new opportunities in asymmetric catalysis.

Transition metal-catalyzed couplings of organic electrophiles with Grignard reagents ("Kumada reactions") were among the first cross-coupling processes that were discovered.^{1,2} Like other families of cross-couplings, this versatile method for the synthesis of carbon-carbon bonds has been applied primarily to reactions of aryl and vinyl electrophiles.³ It is nevertheless noteworthy that the earliest successes in cross-coupling *alkyl* electrophiles were Kumada-type reactions with Grignard reagents.^{4,5,6} Despite that initial progress, to date there have been no examples of *enantioselective* Kumada couplings of *alkyl* electrophiles.^{7,8,9} In this report, we begin to address this challenge, establishing that a Ni/bis(oxazoline) catalyst achieves asymmetric cross-couplings of α -bromoketones with aryl Grignard reagents (eq 1).^{10,11}



With respect to enantioselective cross-coupling reactions of alkyl electrophiles, pybox ligands have proved to be useful for an array of nickel-catalyzed Negishi reactions, whereas 1,2-diamine ligands have found application in Hiyama and Suzuki reactions.⁸ Unfortunately, none

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of the previously described methods achieves the asymmetric Kumada coupling illustrated in entry 1 of Table 1 in good ee and yield.

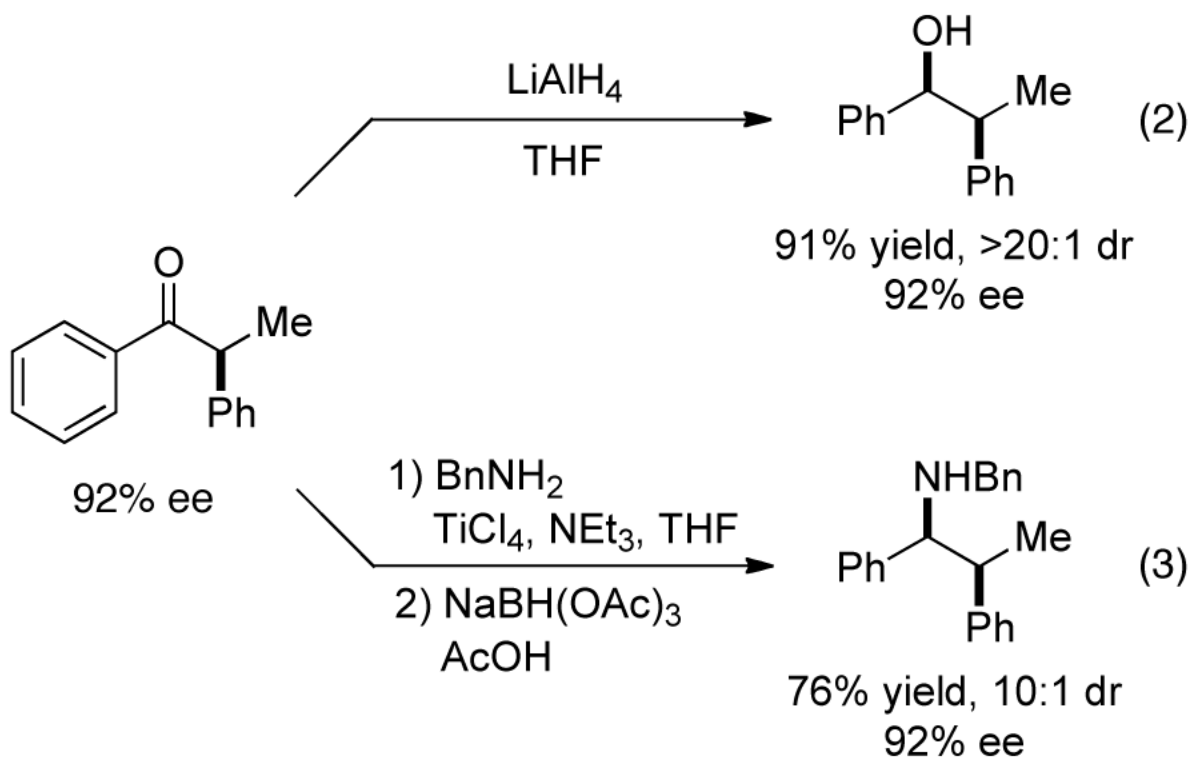
Although bis(oxazoline) ligands have been widely applied in metal-catalyzed processes,¹² to the best of our knowledge they have not been employed in cross-coupling reactions of alkyl electrophiles. We have determined that, in the presence of an appropriate C_2 -symmetric bis(oxazoline), the desired Kumada coupling proceeds both in good yield and with high enantioselectivity (entry 1 of Table 1; $NiCl_2$ -glyme and ligand **1** are commercially available).

Several features of this asymmetric Kumada reaction are noteworthy. First, the cross-coupling is stereoconvergent: both enantiomers of the electrophile are converted efficiently into the same enantiomer of the product.⁸ Second, the reaction occurs at $-60\text{ }^{\circ}\text{C}$, the lowest temperature that has been employed to date for a cross-coupling of an alkyl electrophile (activated or unactivated).¹³ Third, as a consequence of the low temperature, the potentially labile α -arylketone product is not racemized under the Brønsted-basic conditions.¹⁴

Exploiting a procedure developed by Knochel for the synthesis of functionalized Grignard reagents,¹⁵ we have demonstrated that a wide array of aryl Grignards can be employed in our enantioselective Kumada cross-couplings (Table 1).^{16,17} The method is compatible with a diverse spectrum of functional groups, including esters, halides (no aryl-aryl coupling), nitriles, ethers, and heteroaromatic rings (e.g., benzofurans and indoles).¹⁸ Regardless of the electron-withdrawing or electron-donating nature of the substituent on the aromatic ring, consistently good ee's and yields are obtained.

A variety of α -bromoketones are suitable electrophilic partners in this catalytic asymmetric Kumada cross-coupling process. In the case of aryl alkyl ketones (Table 2), the aromatic group can be electron-rich or electron poor, and it can bear a variety of substitution patterns (entries 1-6). Furthermore, the coupling proceeds smoothly with a heteroaromatic substituent (entry 7), as well as with an array of functionalized alkyl groups (entries 9-11). The cross-coupling products can be derivatized with good diastereoselectivity without racemization (eq 2 and 3).¹⁹

When the same conditions are applied to asymmetric Kumada reactions of dialkyl ketones, more modest enantioselectivities are observed (for entry 1 of Table 3, 23% ee and 24% yield). However, by modifying the structure of the bis(oxazoline) and raising the reaction temperature, we have obtained promising ee's for a variety of reaction partners (Table 3). To the best of our knowledge, with a single exception,²⁰ there had been no previous progress in such catalytic asymmetric cross-couplings of dialkyl ketones.



Some preliminary observations may be useful in contemplating the mechanism for this process. A kinetic study of the cross-coupling of 2-bromo-1-phenylpropan-1-one with PhMgBr (entry 1 of Table 1) revealed that the rate law for the reaction is first order in nickel, first order in PhMgBr , and zero order in the electrophile.²¹ In addition, the unreacted electrophile is essentially racemic throughout the course of the reaction (<5% ee; no evidence for kinetic resolution). Finally, the ee of the product correlates linearly with the ee of the ligand (no non-linear effect).

In summary, we have described the first asymmetric Kumada reactions of alkyl electrophiles, specifically, couplings of racemic α -bromoketones with aryl Grignard reagents. This adds to the small but growing list of cross-couplings of alkyl electrophiles that can be achieved with useful enantioselectivity. Several features of this investigation are noteworthy. First, the couplings proceed at remarkably low temperature (-40°C or -60°C), which enables the asymmetric synthesis of racemization-prone α -arylketones. Second, *dialkyl* ketones undergo enantioselective coupling in good ee and yield. Third, readily available bis(oxazolines) have been shown for the first time to be effective ligands for cross-couplings of alkyl electrophiles, thereby opening the door to exciting new opportunities in asymmetric catalysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

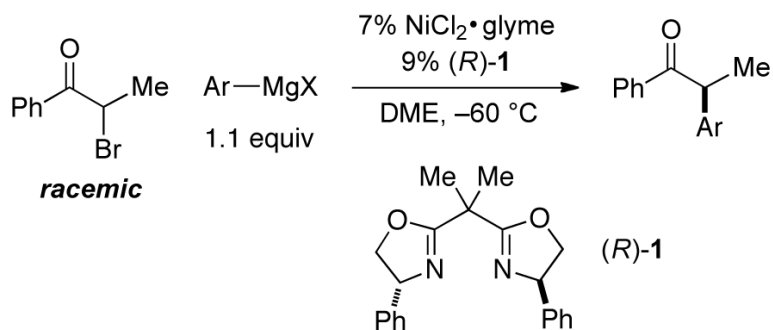
Acknowledgments

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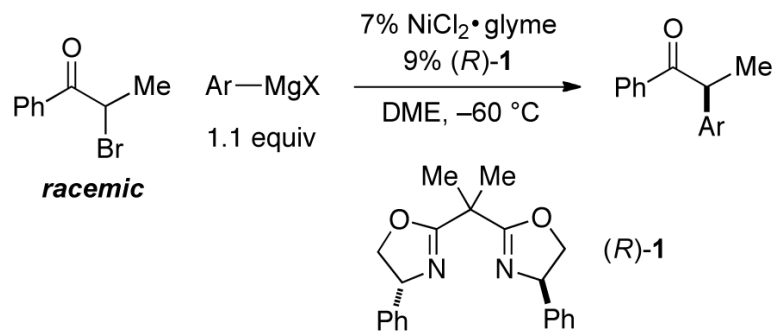
References

- (1). For a historical overview, see: Seyferth D. *Organometallics* 2009;28:1598–1605.
- (2). For pioneering studies of nickel-catalyzed processes, see: (a) Tamao K, Sumitani K, Kumada M. *J. Am. Chem. Soc.* 1972;94:4374–4376. (b) Corriu RJP, Masse JP. *Chem. Commun* 1972:144.
- (3). For overviews of cross-coupling chemistry, see: (a) de Meijere, A.; Diederich, F., editors. *Metal-Catalyzed Cross-Coupling Reactions*. Wiley-VCH; New York: 2004. (b) Miyaura, N., editor. *Topics in Current Chemistry*. Vol. 219. Springer-Verlag; New York: 2002.
- (4). For example, see: Tamura M, Kochi J. *Synthesis* 1971:303–305.
- (5). For some recent work on nickel-catalyzed Kumada reactions of alkyl electrophiles (including leading references), see: (a) Terao J, Kambe N. *Acc. Chem. Res* 2008;41:1545–1554. [PubMed: 18973349] (b) Vechorkin O, Proust V, Hu X. *J. Am. Chem. Soc* 2009;131:9756–9766. [PubMed: 19552426]
- (6). For reviews of cross-coupling reactions of alkyl electrophiles, see: (a) Rudolph A, Lautens M. *Angew. Chem., Int. Ed* 2009;48:2656–2670. (b) Frisch AC, Beller M. *Angew. Chem., Int. Ed* 2005;44:674–688. (c) Netherton, MR.; Fu, GC. *Topics in Organometallic Chemistry: Palladium in Organic Synthesis*. Tsuji, J., editor. Springer; New York: 2005. p. 85–108. (d) Netherton MR, Fu GC. *Adv. Synth. Catal* 2004;346:1525–1532.
- (7). For some leading references to asymmetric cross-couplings of *aryl* and *vinyl* electrophiles, see: (a) Hayashi, T. *Handbook of Organopalladium Chemistry for Organic Synthesis*. Negishi, E.-i., editor. Wiley Interscience; New York: 2002. Chapter III.2.16 (this review also discusses nickel-catalyzed processes) (b) Bermejo A, Ros A, Fernandez R, Lassaletta JM. *J. Am. Chem. Soc* 2008;130:15798–15799. [PubMed: 18980320]
- (8). For examples of catalytic enantioselective cross-coupling reactions of activated and unactivated alkyl electrophiles with other families of nucleophiles, see: (a) Fischer C, Fu GC. Negishi alkylation of α -bromoamides. *J. Am. Chem. Soc* 2005;127:4594–4595. [PubMed: 15796523] (b) Arp FO, Fu GC. Negishi alkylation of benzylic halides. *J. Am. Chem. Soc* 2005;127:10482–10483. [PubMed: 16045323] (c) Son S, Fu GC. Negishi alkylation of allylic chlorides. *J. Am. Chem. Soc* 2008;130:2756–2757. [PubMed: 18257579] (d) Dai X, Strotman NA, Fu GC. Hiyama arylation and vinylation of α -bromoesters. *J. Am. Chem. Soc* 2008;130:3302–3303. [PubMed: 18302392] (e) Caeiro J, Sestelo JP, Sarandeses LA. alkynylation of benzylic bromides. *Chem. Eur. J* 2008;14:741–746. (f) Saito B, Fu GC. Suzuki alkylation of homobenzylic bromides. *J. Am. Chem. Soc* 2008;130:6694–6695. [PubMed: 18447357] (g) Smith SW, Fu GC. Negishi arylation of propargylic halides. *J. Am. Chem. Soc* 2008;130:12645–12647. [PubMed: 18763769] (h) Lundin PM, Esquivias J, Fu GC. Negishi arylation of α -bromoketones. *Angew. Chem., Int. Ed* 2009;48:154–156.
- (9). For an overview of asymmetric cross-couplings of secondary alkyl halides, see: Glorius F. *Angew. Chem., Int. Ed* 2008;47:8347–8349.
- (10). For leading references to target molecules that include ketones that bear an α -aryl group, see: Fox JM, Huang X, Chieffi A, Buchwald SL. *J. Am. Chem. Soc* 2000;122:1360–1370.
- (11). The catalytic enantioselective synthesis of α -arylketones that bear *tertiary* stereocenters has not been achieved via the cross-coupling of ketone enolates with aryl electrophiles, due to racemization of the product under the Brønsted-basic reaction conditions. For key studies and discussions regarding the catalytic asymmetric synthesis of α -arylketones that bear *quaternary* stereocenters, see: (a) Åhman J, Wolfe JP, Troutman MV, Palucki M, Buchwald SL. *J. Am. Chem. Soc* 1998;120:1918–1919. Hamada T, Chieffi A, Åhman J, Buchwald SL. *J. Am. Chem. Soc* 2002;124:1261–1268. [PubMed: 11841295] (b) Liao X, Weng Z, Hartwig JF. *J. Am. Chem. Soc* 2008;130:195–200. [PubMed: 18076166] (c) Chen G, Kwong FY, Chan HO, Yu W-Y, Chan ASC. *Chem. Commun* 2006:1413–1415.
- (12). For examples and leading references, see: Hargaden GC, Guiry PJ. *Chem. Rev* 2009;109:2505–2550. [PubMed: 19378971]
- (13). To the best of our knowledge, the lowest temperature previously employed for a cross-coupling of an alkyl electrophile was $-30\text{ }^{\circ}\text{C}$ (Reference 8h).
- (14). Although no racemization of the product occurs after 24 hours at $-60\text{ }^{\circ}\text{C}$, significant racemization is observed at room temperature.

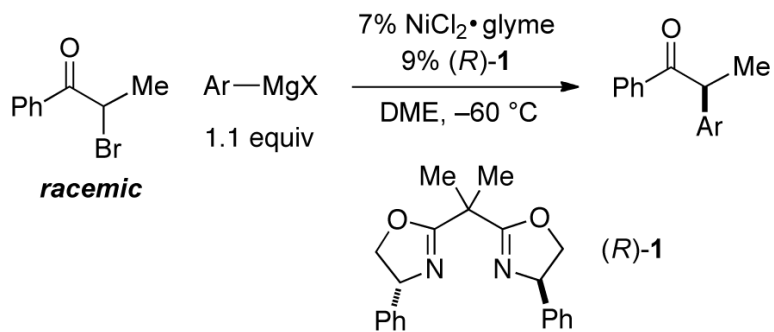
- (15). (a) Boymond L, Rottländer M, Cahiez G, Knochel P. *Angew. Chem., Int. Ed* 1998;37:1701–1703. For a review, see: (b) Knochel P, Dohle W, Gommermann N, Kneisel FF, Kopp F, Korn T, Sapountzis I, Vu VA. *Angew. Chem., Int. Ed* 2003;42:4302–4320.
- (16). Notes: (a) For the cross-coupling illustrated in entry 1 of Table 1: on a gram-scale (5% NiCl₂-glyme/6.5% bis(oxazoline)), the reaction proceeds in 92% ee and 80% yield; no carbon–carbon bond formation is observed in the absence of NiCl₂-glyme (NiBr₂-glyme or Ni(cod)₂ may be used in place of NiCl₂-glyme); in the absence of the bis(oxazoline) ligand, the product is generated in 22% yield; the ee of the product is constant during the cross-coupling; in a competition experiment, an unactivated alkyl bromide is recovered in essentially quantitative yield; and, use of a solution of the Grignard reagent in THF results in somewhat lower ee and yield. (b) The efficiency of this method is sensitive to the steric demand of the coupling partners. (c) α -Chloroketones are not suitable substrates under these conditions.
- (17). *Sample experimental procedure*: A 20-mL vial equipped with a stir bar was capped with a septum and taped. The vial was purged with argon for 2 min, and then 1,2-dimethoxyethane (8 mL) was added by syringe, followed by the aryl iodide (1.10 mmol). The solution was cooled to –20 °C, and a solution of *i*-PrMgCl (2.0 M solution in Et₂O; 0.55 mL, 1.1 mmol) was added over 1 min. The resulting mixture was stirred at –20 °C for 1–2 h, and then it was cooled to –60 °C. Ligand (*R*)-**1** (30.0 mg, 0.090 mmol) and NiCl₂-glyme (15.3 mg, 0.070 mmol) were added to a 4-mL vial equipped with a stir bar. The vial was capped with a septum, taped, and gently purged with argon for 1 min. 1,2-Dimethoxyethane (2.0 mL) was added, and this solution of the catalyst was stirred at room temperature for 5 min. Next, the α -bromoketone (1.0 mmol) was added, and the mixture was stirred at room temperature for 5 min. Then, the resulting homogeneous dark-pink solution was added dropwise over 3 min to the –60 °C solution of the Grignard reagent. The resulting yellow solution was stirred at –60 °C for 16–32 h. Next, the reaction was quenched with ethanol (2 mL), and the resulting mixture was filtered through a Büchner funnel that contained a bed of silica gel. The silica gel was washed with Et₂O (40 mL), and the combined filtrates were concentrated by rotary evaporation. The resulting residue was purified by flash chromatography.
- (18). Under our standard conditions, our initial attempts to couple heteroaromatic Grignard reagents such as 2-pyridylmagnesium chloride and 3-thienylmagnesium chloride were not successful.
- (19). For previous examples, see: (a) Cram DJ, Elhafez FAA. *J. Am. Chem. Soc* 1952;74:5828–5835. (b) Vicario JL, Badia D, Dominguez E, Carrillo L. *J. Org. Chem* 1999;64:4610–4616. [PubMed: 11674530]
- (20). See footnote 18 in Reference ^{8h}.
- (21). This rate law can be accommodated by a reaction pathway proposed by Vicic: (a) Jones GD, Martin JL, McFarland C, Allen OR, Hall RE, Haley AD, Brandon RJ, Konovalova T, Desrochers PJ, Pulay P, Vicic DA. *J. Am. Chem. Soc* 2006;128:13175–13183. [PubMed: 17017797] (b) Lin X, Phillips DL. *J. Org. Chem* 2008;73:3680–3688. [PubMed: 18410144]

Table 1Asymmetric Kumada Reactions of α -Bromoketones: Variation of the Nucleophile

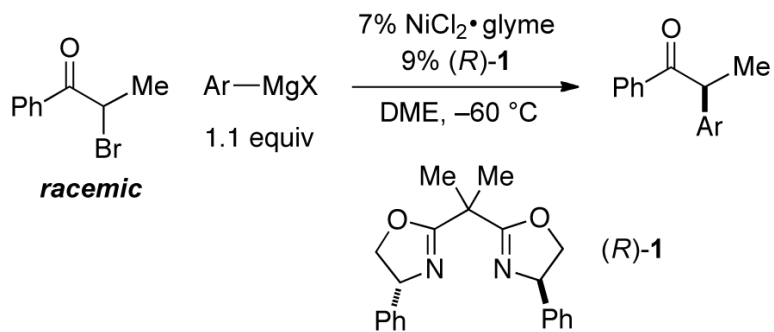
entry	Ar	ee (%)
1	Ph	92
2		80
3	X = Br CN OMe	93
4		95
5		92
6	X = CF ₃ CO ₂ Et I OMe	94
7		95
8		94
9		91



entry	Ar	ee (%)
10		95



entry	Ar	ee (%)
11		92
12		91



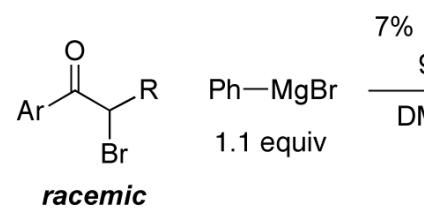
entry	Ar	ee (%)
13		90

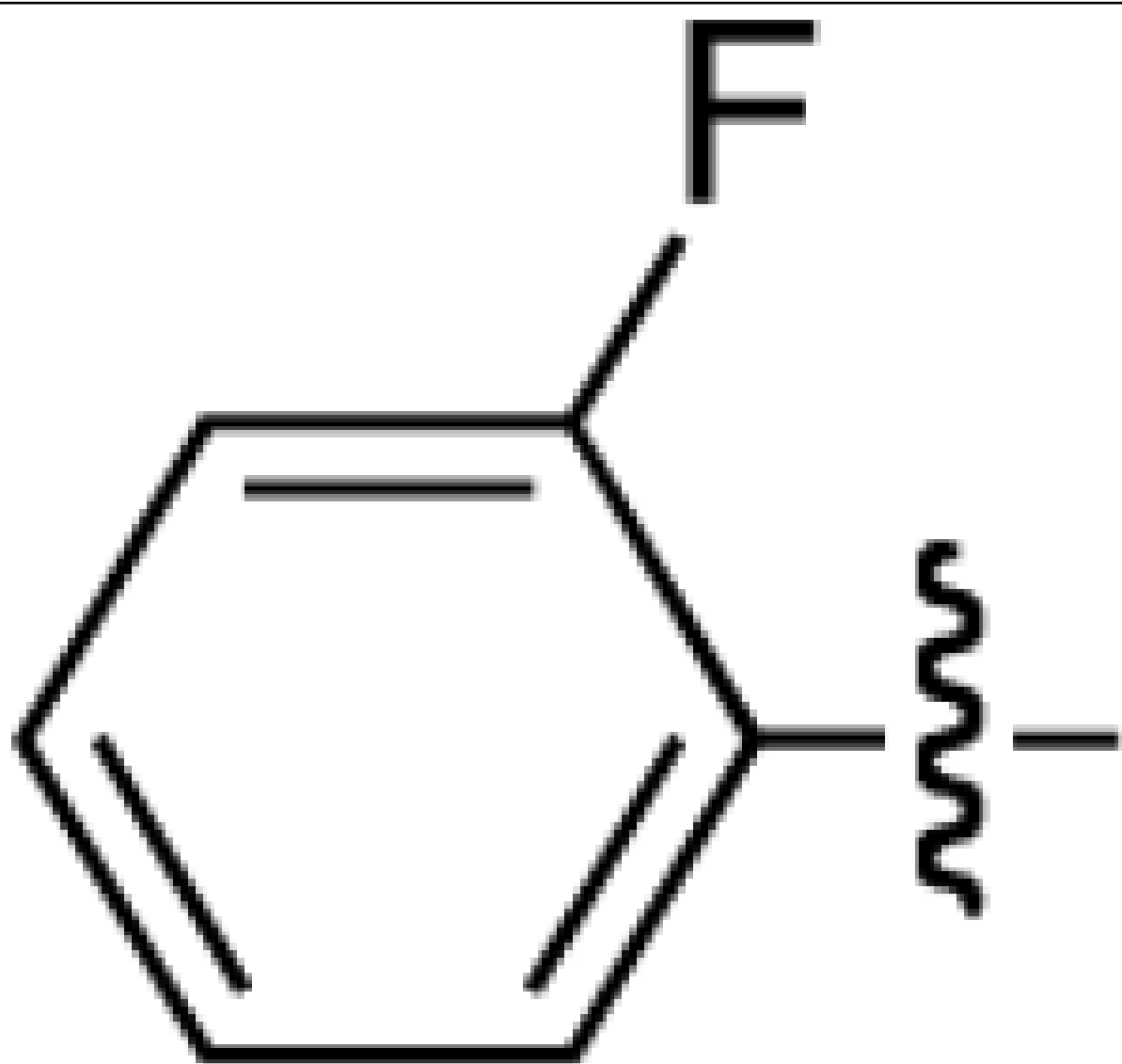
All data are the average of two experiments.

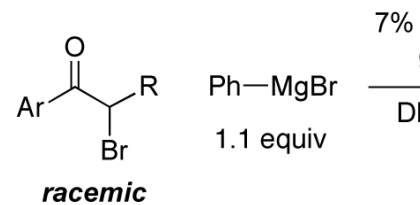
^aYield of purified product.

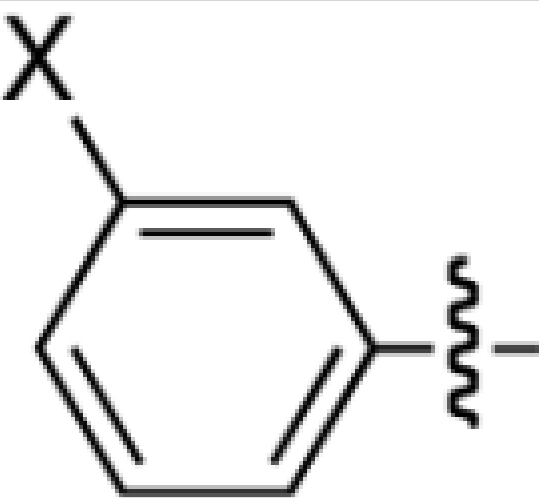
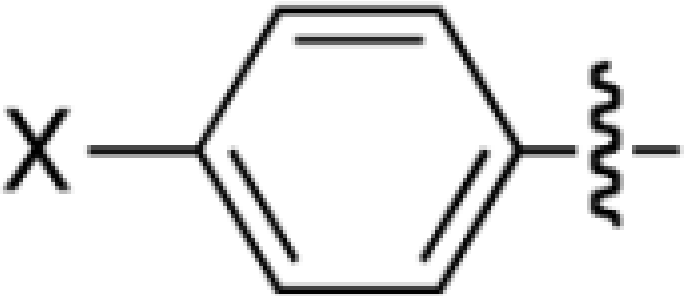
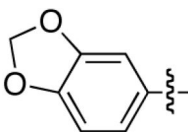
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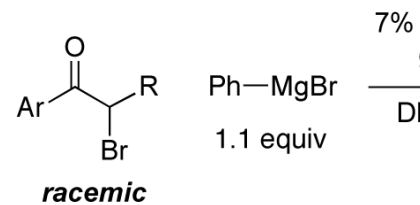
Asymmetric Kumada Reactions of Aryl Alkyl Ketones

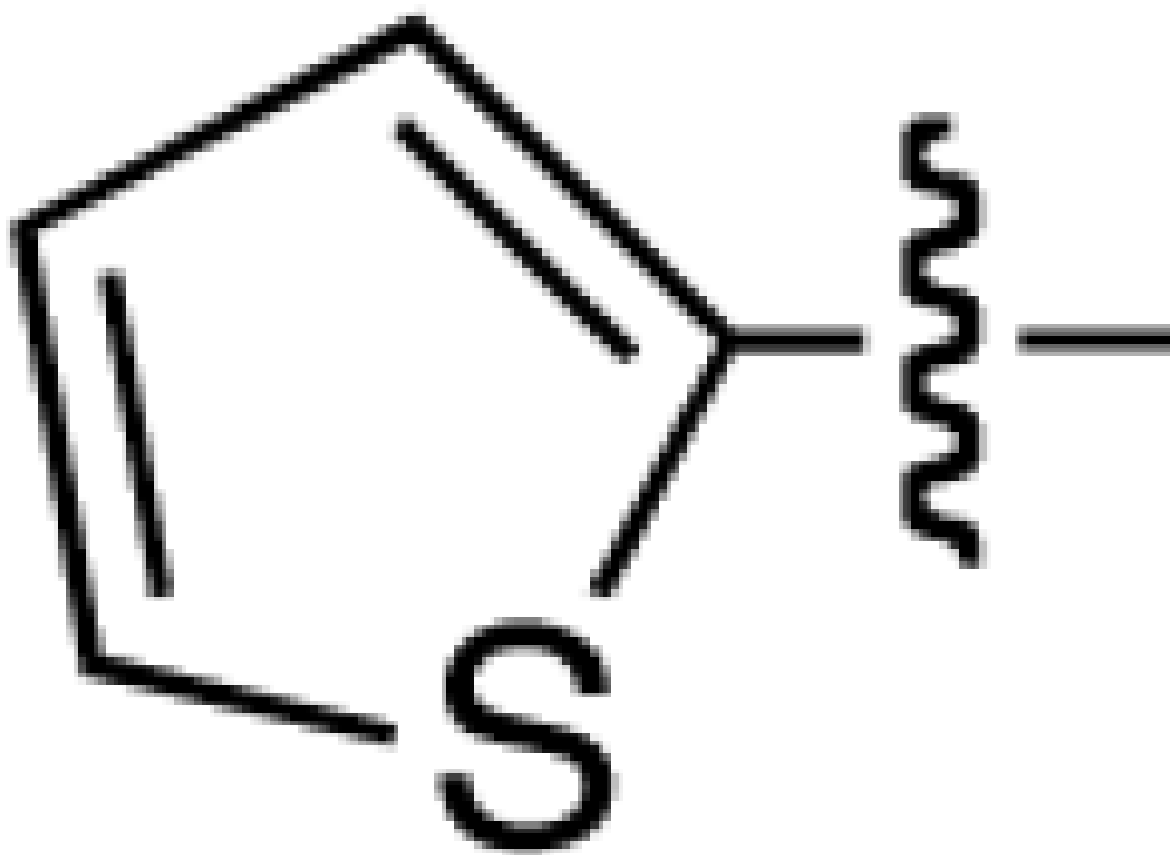


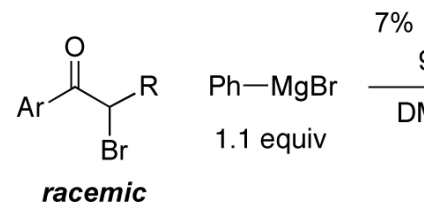
entry	Ar
1	



entry	Ar
2	 X = Cl OMe
3	
4	
5	 X = Br OBn
6	



entry	Ar
7	
8	Ph
9	Ph



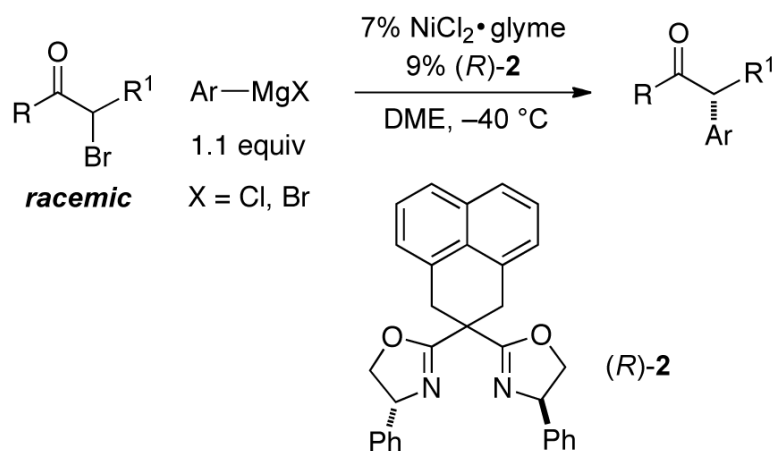
entry	Ar
10	Ph
11	Ph

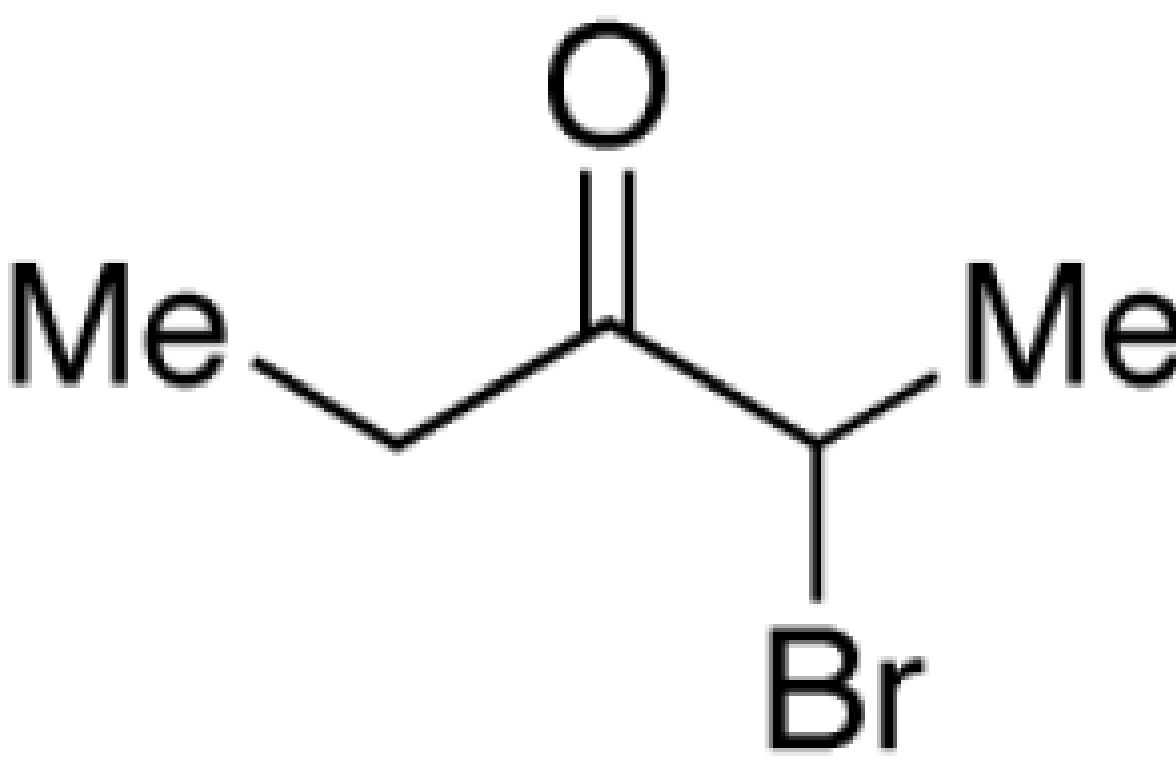
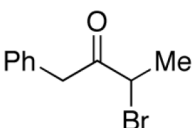
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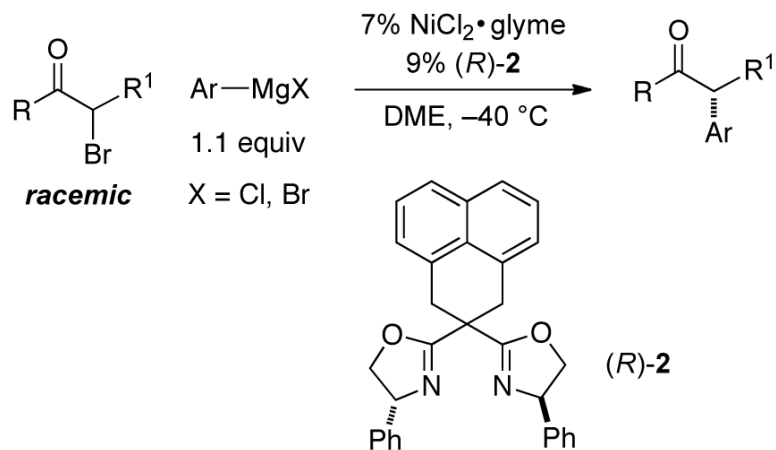
^aYield of purified product.

Table 3

Asymmetric Kumada Reactions of Dialkyl Ketones



entry	ketone	Ar
1		Ph
2		Ph
3		4-Cl-C ₆ H ₄
4		4-CO ₂ Et-C ₆ H ₄
5		4-OMe-C ₆ H ₄

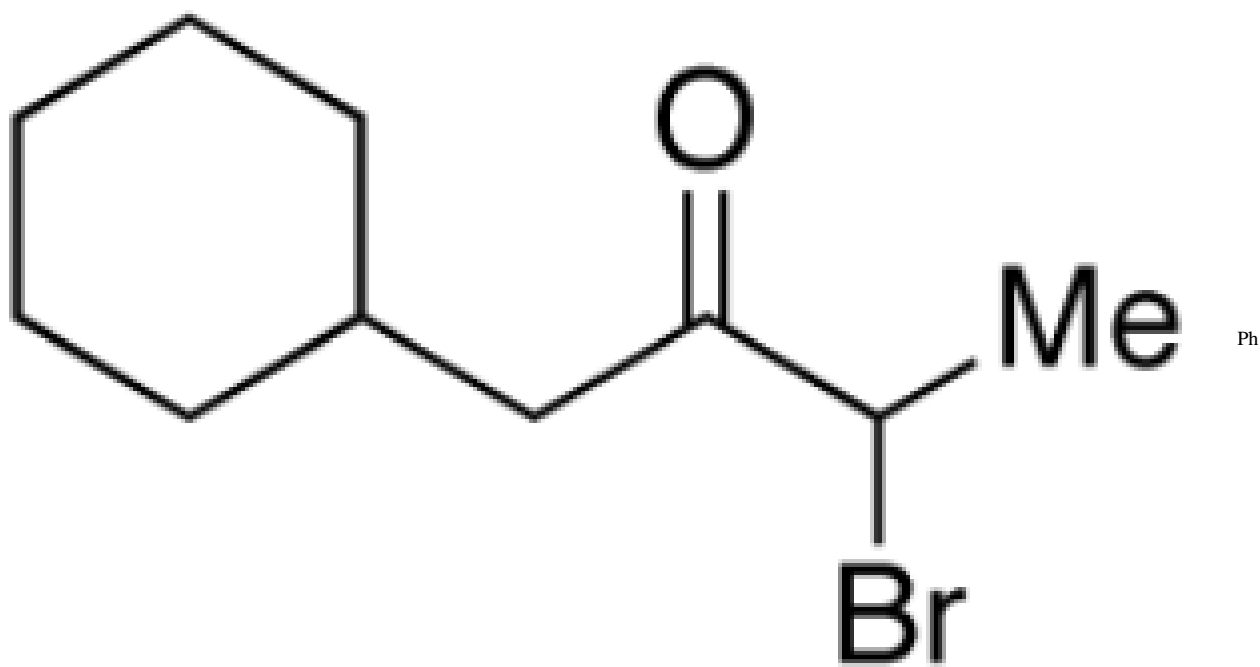


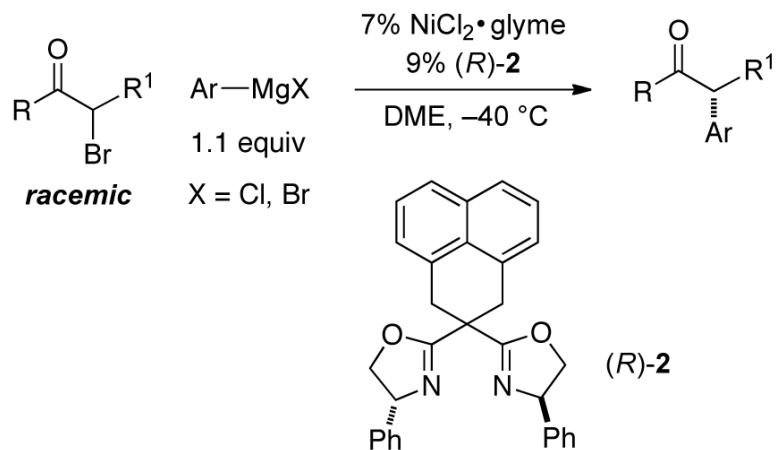
entry

ketone

Ar

6



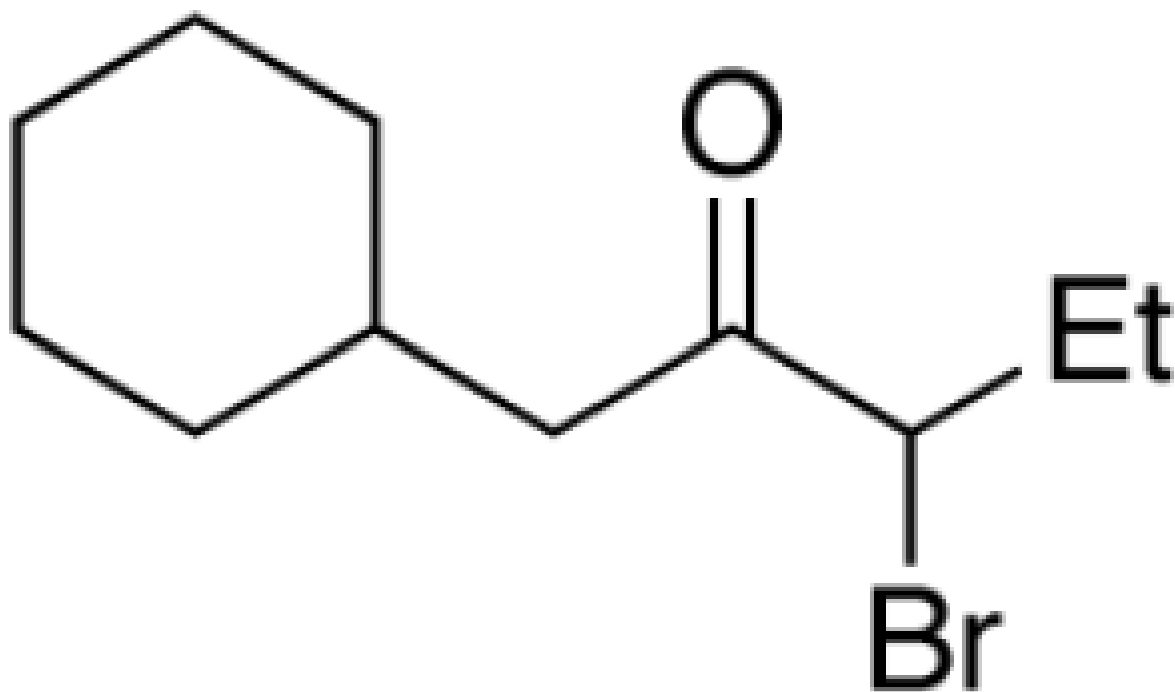


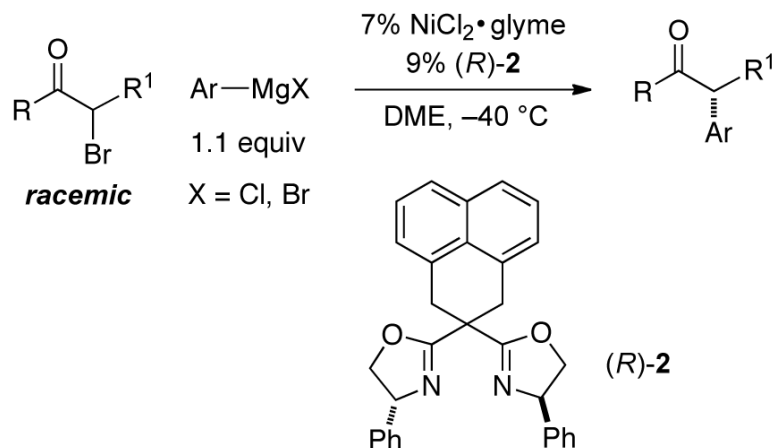
entry

ketone

Ar

7

3-Br-C₆H₄



entry

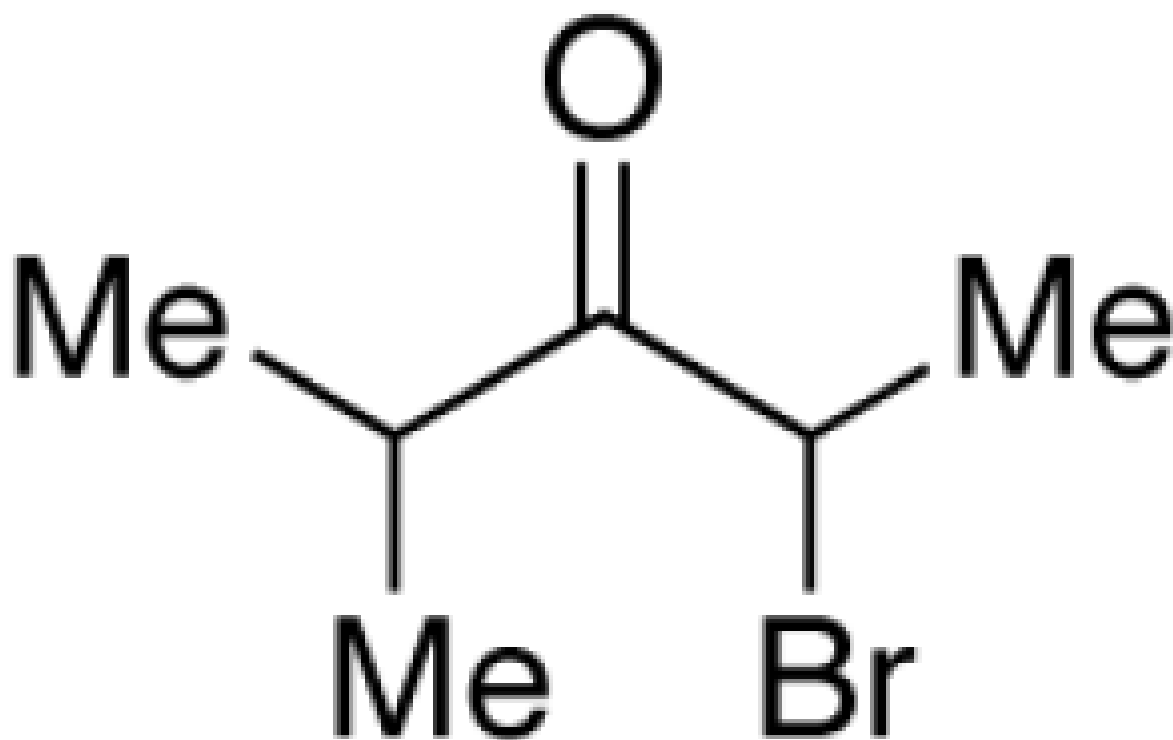
ketone

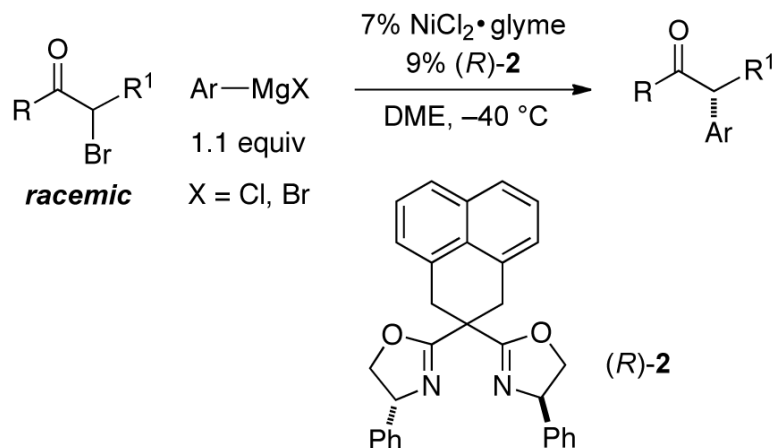
Ar

8

Ph

9

3,4-OCH₂

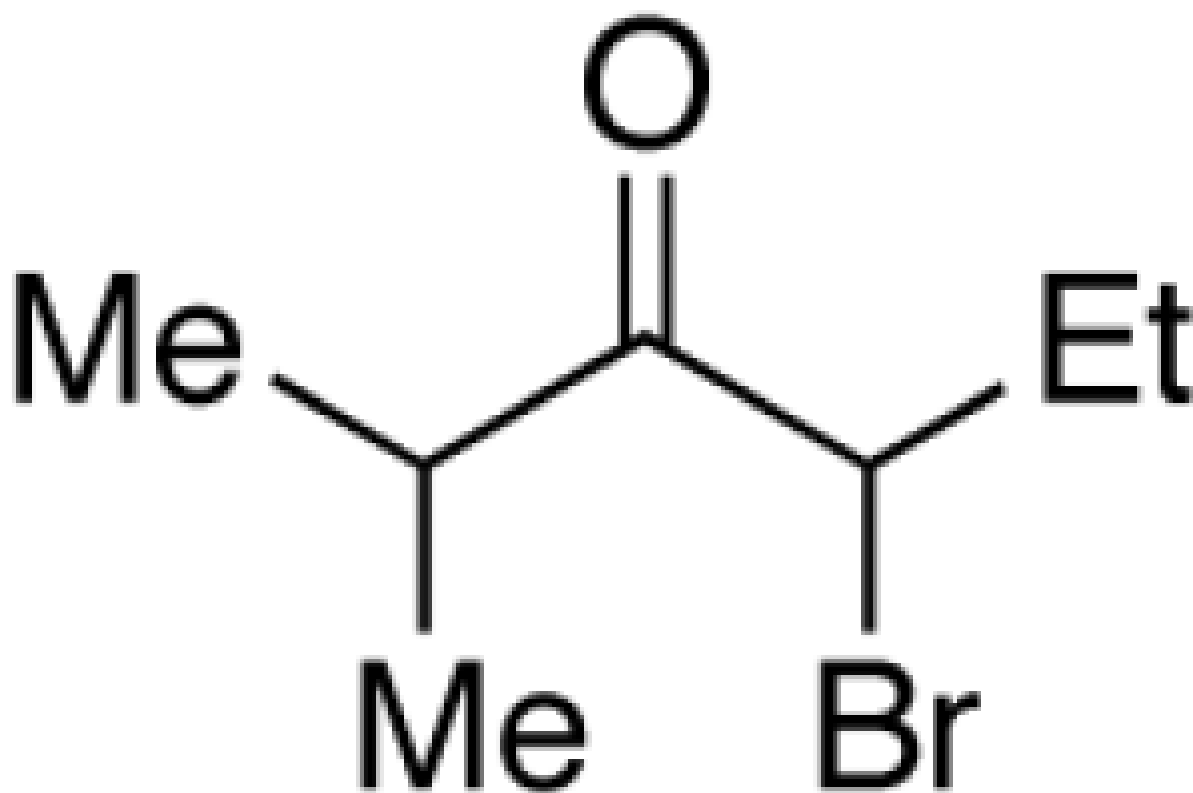


entry

ketone

Ar

10

4-CO₂Et-

All data are the average of two experiments.

^aYield of purified product.